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REGULAR ARTICLES

Ischaemia reperfusion may be a new approach in cancer interventional therapy

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KEYWORDS

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Hypothesis

Abstract Cancer is a leading cause of death worldwide. Interventional cancer therapy made huge progress in the past few decades; however, traditional interventional therapy, for example, transarterial embolisation and transarterial chemoembolisation, remains to be developed for its potential limitations. Numerous studies in the past half century demonstrated that tissue injury accelerated after ischaemia reperfusion. Reactive oxygen species (ROS) production, cell death and inflammatory factors involved in the development of ischaemia reperfusion injury. As outlined above, we hypothesise that reperfusing the tumour lesion with high oxygen, high calcium and high pH fluid together with ROS-generating agents and/or inhibitor of antioxidant system, with or without traditional chemotherapeutic agents after a short-time arterial embolisation, can effectively induce cancer cell death, and it might be a new attempt in cancer interventional therapy.

Introduction

Cancer is a leading cause of death worldwide. Billions of dollars were spent on exploring the effective strategy for cancer treatment, but the output remains clearly dissatisfied. Traditionally, there are three pillars in the treatment of malignant tumour: chemotherapy, radiotherapy and surgery. In the past few decades, interventional therapy rapidly developed in very early local cancer treatment and advanced cancer palliative care for its obvious advantages such as minimal invasion [1]. Arterial chemotherapy and lipiodolisation directly deliver a highly concentrated dose of chemotherapeutical drugs to tumour tissues, to prolong the contact time between the drugs and the tumour cells and to minimise systemic toxicity from the chemotherapeutic agents [2]. Arterial chemotherapy and lipiodolisation were earlier applied in clinical treatment of cancer, but they have nearly been replaced by transarterial embolisation (TAE) and transarterial chemoembolisation (TACE) during the last decade, which was demonstrated by their effectiveness proved by randomised clinical trials [2,3].

TAE is one of the most frequently used interventional therapy techniques. Theoretically, embolisation can be performed

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in any area of the body. This technique can be performed preoperatively or as a palliative means [1]. The mechanism of TAE is induction of tumour ischaemia necrosis and programmed cell death through blocking the tumour blood and oxygen supply. TACE is an improved TAE and it refers to the same procedure preceded by the administration of chemotherapeutic agents. Although there exist controversial findings, more researchers incline to support that effectiveness of TAE together with regional chemotherapy is better than simple arterial chemoperfusion in cancer treatment [1,3]. However, recent data suggested that hypoxia generated by arterial embolisation up-regulated vessel endothelial growth factor (VEGF) and induced angiogenesis that leads to tumour growth [4]. Moreover, studies have shown that hypoxia mediates cancer cells resisting apoptosis [5,6]. Furthermore, by an unknown mechanism hypoxia is associated with metastasis [7]. Therefore, it is necessary to improve TACE or explore new methods of transarterial therapy.

In the 1960s, Jennings et al. reported that canine heart subjected to coronary ligation showed reperfusion appearing to accelerate the development of necrosis [8]. In the following half century, ischaemia reperfusion injury (IRI) was profoundly explored. Although the essential mechanisms remain unclear, accelerated injury of ischaemic tissues after reperfusion is unquestionable. Ischaemia leads to tissue acidosis and accumulation of intracellular sodium, hydrogen and calcium ion. Reperfusion elicits rapid renormalisation of intracellular sodium, hydrogen, calcium and hypoxia and consequently results in the so-called oxygen paradox, calcium paradox and pH paradox [9]. Molecular and cellular events such as reactive oxygen species (ROS) production, cell death, leucocyte invasion and innate immune reaction play critical roles in the development of ischaemia reperfusion injury [9–11].

The hypothesis

Considering that ischaemia reperfusion may lead to injury in normal organs, especially those with high metabolic rate, it is reasonable to assume that ischaemia reperfusion can also lead to tumour injury. Therefore, we hypothesise that reperfusing the tumour lesion with high oxygen, high calcium concentration and high pH fluid together with ROS-generating agents and/or inhibitor of antioxidant system, with or without traditional chemotherapeutic agents after a short-time (60 min) arterial embolisation, will be an effective candidate for interventional therapy for cancer treatment. Considering the achievement done and the obstacles faced by tumour interventional therapy, we believe that this is a totally new approach that is worth attempting.

Evaluation of the hypothesis

Excessive amounts of ROS induce cancer cell death by directly damaging membranes, DNA and proteins, and/or induce cell apoptosis [12]. ROS as target in cancer treatment was widely detected and believed to be a promising therapy [13,14]. Most recently, *Nature Review Drug Discovery* published an article claiming that targeting cancer cell by ROS-mediated mechanism is probably a radical therapeutic approach [12]. Several ROS-generating agents and inhibitors of antioxidant system are currently in clinical trial [12,15–17]. Although a great diversity of factors involved in the development of IRI, ROS generation was recognised as one of the most critical ones [18]. Reperfusing ischaemic tumour tissue with perfusate containing ROS-generating agents and/or inhibitors of antioxidant system, with or without traditional chemotherapeutic drugs, may theoretically induce more ROS generation and damage tumour cells. Cancer stem cells (CSCs) are cancer cells that possess the characteristics associated with normal stem cells, and CSCs may generate tumour by self-renewal and differentiation [19]. CSCs are naturally resistant to chemotherapeutic agents because of their slow rate of cell turnover, DNA repair protein and various pumps that pump out drugs [20]. Recent research found that CSCs show low ROS level, and pharmacological depletion of ROS scavengers in CSCs markedly decrease their clonogenicity and result in radiosensitisation. Overcoming low ROS level of CSCs may be a promising approach for improving local and systemic oncological therapies [21]. Moreover, cancer cell mitochondria are structurally and functionally different from their normal counterparts, thereby rendering them more susceptible to mitochondrial perturbations than non-immortalised cells [22]. Cell death occurs via necrosis and apoptosis after ischaemia reperfusion. Mitochondria play a critical role in these two distinct types of death [9,23]. Thereafter, we reason that reperfusing tumour tissue after an appropriate ischaemia procedure will induce effective cancer cell death.

Furthermore, up-regulated cytokine, activated innate immunity, neutrophil accumulation and macrophage/T-cell-mediated injury after ischaemia reperfusion are all involved in cancer cell death [9,11].

Taken together, we assume that ischaemia reperfusion of tumour tissue with ROS-generating agents and/or inhibitors of antioxidant system, with or without traditional chemotherapeutic drugs, could be more effective in treating cancer than both simply transarterial embolisation and arterial chemotherapy.

Testing the hypothesis

We recommend the following procedure to test the hypothesis:

1. Establish malignant animal model. Abdominal viscera such as liver or kidney cancers are good models because they have a single blood vessel supply and less collateral circulation which facilitate ischaemia reperfusion. (95% blood supply to primary hepatic carcinoma by hepatic artery, almost 100% blood supply to kidney cancer by renal artery).
2. Compare the outcomes between arterial embolisation (ischaemia) and recanalisation after arterial embolisation 60 min (ischaemia reperfusion) in the following aspects: A, tumour growth; B, tumour metastasis; C, survival rate; D, biopsy detection of tumour cells death; E, radiosensitivity, chemosensitivity and operation opportunity.
3. Compare the outcomes between arterial embolisation and reperfusion after arterial embolisation 60 min with ROS-generating agents and/or inhibitors of antioxidant system, with or without traditional chemotherapeutic drugs.
4. Evaluate the therapeutic effects in different ischaemia reperfusion times (30′, 60′, 90′ and 120′) and frequencies 1, 2 and 4.

Conflict of interest statement

None declared.

Overview Box

First Question: What do we already know about the subject?

1. Ischaemia leads to tissue damage.
2. Tissue injury accelerated after ischaemia reperfusion.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

Ischaemia reperfusion may accelerate tumour tissue injury. This hypothesis provides a new essay in tumour treatment.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

The hypothesis can be tested conducting by animal experiments. We can compare the outcomes of embolisation and recanalisation after arterial embolisation, and then observe multiple end-point events including tumour growth, metastasis and animal survival time, etc.

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